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NATIONAL INSTITUTE OF MENTAL HEALTH

National Advisory Mental Health Council

Minutes of the 204th Meeting

September 12, 2003

Minutes of the 204th Meeting of the National Advisory Mental Health Council

The National Advisory Mental Health Council (NAMHC) convened its 204th meeting in closed session for the purpose of reviewing grant applications at 10:30 a.m. on September 11, 2003, in the Neuroscience Center, Rockville, Maryland, and adjourned at approximately 5:30 p.m. (see Appendix A: Review of Applications). The NAMHC reconvened in open session at 8:30 a.m. on September 12, 2003, on the main campus of the National Institutes of Health (NIH), Bethesda, Maryland. In accordance with Public Law 92-463, this policy meeting was open to the public until its adjournment at 12:45 p.m. Thomas R. Insel, M.D., Director, National Institute of Mental Health (NIMH), chaired the meeting.

Council Members Present at Closed and/or Open Sessions (see Appendix B for the Council Roster)

Robert O. Boorstin
Javier I. Escobar, M.D.
Susan M. Essock, Ph.D.
Susan Folkman, Ph.D.
Megan R. Gunnar, Ph.D.
Renata J. Henry
Henry A. Lester, Ph.D.
Jeffrey A. Lieberman, M.D.
James L. McClelland, Ph.D.
James P. McNulty
Eric J. Nestler, M.D., Ph.D.
Charles F. Reynolds, III, M.D.
Elaine Sanders-Bush, Ph.D.
Larry R. Squire, Ph.D.
Ming T. Tsuang, M.D., Ph.D.
Karen Dineen Wagner, M.D., Ph.D.

Chairperson

Thomas R. Insel, M.D.

Executive Secretary

Jane A. Steinberg, Ph.D.

Ex-Officio Council Members Present

Elspeth Cameron Ritchie, M.D., Department of Defense
Robert Freedman, M.D., Department of Veterans Affairs

Liaison Representative, Substance Abuse and Mental Health Services Administration

Neal Brown, M.P.A., Center for Mental Health Services

Others Present at Open Policy Session
Michelle Alonso, Anxiety Disorders Association of America
Jane Browning, Learning Disabilities Association
Judith Cornelius, Child and Adolescent Bipolar Foundation

Marian Cremin, Treatment and Research Advancements-National Association for Personality Disorder
Megan Cundarf, American Hospital Association
Chris deVries, American Association for Geriatric Psychiatry
Deborah DiGilio, American Psychological Association
Jill Egeth, Federation of Behavioral, Psychological and Cognitive Services
Diane Elmore, American Psychological Association
Janet Emmerman, Obsessive Compulsive Foundation
Chris Erickson, George Washington University
Susan Eveson, Employee Assistance Professionals Association
Robyn Golden, Office of Senator Hillary Rodham Clinton
Barbara Goldman, Society for Neuroscience
Dan Gordon, *Dana Press*
Constance Holden, *Science*
Thomas Horvath, Department of Veterans Affairs
Lara Insel
Scott Jenkins, *The Blue Sheet*
Ira Katz**,** American Geriatrics Society
Ann Kearney-Cooke, Academy for Eating Disorders
Gary J. Kennedy, Montefiore Medical Center, American Association for Geriatric Psychiatry
Ronald Kessler, Harvard Medical School
Alan Kraut, American Psychological Society
Michael P. Lee, Foundation for the NIH
William Narrow, American Psychiatric Association
Martha Nolan, Society for Women's Health Research
William Northey, American Association for Marriage and Family Therapy
Patricia Perkins, Obsessive Compulsive Foundation
Valerie Porr, Treatment and Research Advancements-National Association for Personality Disorder
Stephanie Reed, American Association for Geriatric Psychiatry
Darrel Regier, American Psychiatric Association
Anita Rosen, Council on Social Work Education
Mercedes Rubio, American Sociological Association
M.J. Schumanan, American Nurses Association
Carol Schutz, Gerontological Society of America
Angela Sharpe, Consortium of Social Science Associations
Paul Sirovatka, American Psychiatric Association
Anita Stevens, Circle Solutions, Inc.
Joel E. Streim, American Association for Geriatric Psychiatry
Karen Studwell, American Psychological Association
Liz Thomas, Alliance for Children & Families
Marjorie Vanderbilt, American Association for Geriatric Psychiatry
Barbara Wanchisen, The Federation of Behavioral, Psychological and Cognitive Sciences
Sheldon Weinberg, The CDM Group, Inc.
Karen White, Children and Adults with Attention-Deficit/Hyperactivity Disorder
Richard Yanes, Clinical Social Work Federation
Steven Zarit, American Psychological Association
Joan Zlotnik, Institute for the Advancement of Social Work Research

OPEN POLICY SESSION: Call to Order/Opening Remarks

Thomas R. Insel. M.D., Director, NIMH, and Chairman, NAMHC, convened the open policy session of the 204th Council meeting at 8:30 a.m. on September 12, in Conference Room 6C10, Building 31C, on the campus of the NIH in Bethesda, Maryland. After welcoming those present, Dr. Insel extended a special welcome to Mr. Neal Brown, Acting Director, Division of Service Systems Improvement, Center for Mental Health Services (CMHS), Substance Abuse and Mental Health Services Administration (SAMHSA), who has worked with NIMH staff for over two decades in joint efforts to resolve issues affecting individuals with or at risk for the development of mental illness.

Recognition of Retiring Council Members

Dr. Insel acknowledged the significant contributions of the retiring Council members—Mr. Robert O. Boorstin and Drs. Javier I. Escobar, Henry A. Lester, James L. McClelland, and Elaine Sanders-Bush—and presented each with letters of appreciation from Secretary of Health and Human Services Tommy Thompson.

Approval of the Minutes for the Previous Council Meeting

Dr. Insel requested and received a motion for approval of the minutes for the May 9, 2003, NAMHC meeting, which passed unanimously without further discussion.

NIMH DIRECTOR'S REPORT

Moving to the main agenda, Dr. Insel's remarks focused on four areas: (1) recent reports by the President's New Freedom Commission on Mental Health and the Institute of Medicine (IOM); (2) the NIH Roadmap; (3) two significant scientific discoveries; and (4) a new NIMH initiative.

As background to the first report, Dr. Insel noted that the President's New Freedom Commission on Mental Health was charged with studying the mental health service delivery system and with making recommendations that would enable children and adults with serious mental illnesses to live, work, learn, and participate fully in their communities. The Commission's historic final report, "Achieving the Promise: Transforming Mental Health Care in America" (see http://www.mentalhealthcommission.gov/reports/reports.htm) stresses that recovery from serious mental illness is possible; mental health care should be organized around consumers and families; an improved mental health services delivery system must address the comorbidities that often accompany mental illness; it is critical that all Americans have access to the most current treatments and best support services that lead to recovery and ultimately to preventive interventions; and the science-to-service cycle must be strengthened so that research findings are more rapidly translated into widely disseminated evidence-based practices. A key role for NIMH will be to work with SAMHSA to ensure that people have access to the successful treatments developed through research.

The second report described by Dr. Insel, the congressionally mandated report "Enhancing the Vitality of the NIH: Organizational Change to Meet New Challenges" (see

http://www4.nationalacademies.org/news.nsf), was issued in the summer of 2003 by the IOM and addresses whether the current NIH structure and organization are optimal to meet the scientific needs of the 21st century. Of the 14 recommendations contained in the report, Dr. Insel highlighted 6 that particularly relate to the research activities of NIMH:

1. Enhance and increase trans-NIH strategic planning and funding. The Committee recommended that the NIH Director lead a planning process to identify crosscutting issues and their associated research and training opportunities and to generate a small number of major and time-limited trans-NIH research programs. The recommendation contains language about the need for additional staff to participate in the planning process and to "jump-start" the initiatives that emerge from this process.

2. Strengthen the office of the NIH Director. This would be accomplished by initiating a public process for exploring restructuring of the NIH Institutes/Centers and for the funding of innovative high-risk projects with the potential for high payoffs in advancing scientific knowledge.

3. Promote innovation and risk taking in intramural research. The report notes that the intramural research program is well positioned to support innovative and high-risk research and that its programs must complement and be distinguished from those supported in the extramural community and private sector.

4. Retain integrity in appointments to advisory councils. The Committee recommended setting stringent criteria for selecting advisory council members to ensure the integrity of these bodies and to increase their involvement in setting Institutes' research priorities and reviewing their management practices.

5. Set terms and conditions for both the Institute/Center and NIH Directors. This recommendation is based on the Committee's vision that a healthy turnover in leadership is critical for sustaining the vitality of NIH.

6. Strengthen the overall NIH clinical research effort. The Committee recommended that clinical research at NIH could be enhanced by consolidating several intramural and extramural programs, by partnering with the nonprofit and private sectors, and by creating a new leadership position, the Deputy Director for Clinical Research, in the NIH Office of the Director.

Turning to the NIH Roadmap, Dr. Insel remarked that this planning process has led to several new and exciting trans-NIH research initiatives. The Roadmap's three major thrusts (i.e., new pathways to discovery, building research teams of the future, and re-engineering the clinical research enterprise) parallel many of the recommendations contained in the IOM report described above. NIMH staff members participate on eight of the nine Roadmap implementation groups: (1) Building Blocks and Pathways; (2) Structural Biology; (3) Bioinformatics and Computational Biology; (4) Molecular Libraries and Imaging; (5) Interdisciplinary Research Teams; (6) Public-Private Partnerships; (7) High-Risk Research; and (8) Re-Engineering Clinical Research. The Nanotechnology group is the only one with no NIMH representative.

Dr. Insel described one activity originating in the Molecular Libraries and Imaging group—the molecular libraries initiative. This initiative is designed to overcome the acknowledged limitations in current procedures for developing new drugs. Although there are 30,000 genes and an estimated 200,000 to 300,000 protein targets, there are fewer than 500 marketed gene products for all areas of medicine, and of these, a maximum of 20 are targets for the development of treatments for mental illness. The molecular libraries initiative will focus on expanding the pool of targets by generating new screening approaches and by developing chemical repositories and small molecules that can lead to drug development. Currently, there are almost a million small molecules that could be tested as potential drug candidates. Innovative robotics technologies will permit the rapid screening of these compounds. The NIH budget for this project is about $26 million in fiscal year (FY) 2004, of which $15 million will fund the small molecule library and screening program; $5 million will support cheminformatics, and $6.5 million will be dedicated to technology development. One intramural screening center will be established initially, and a Request for Applications (RFA) will be developed for funding extramural screening centers. Dr. Insel reported that he and Dr. Francis Collins, Director, National Human Genome Research Institute (NHGRI), are leading this initiative. Dr. Insel acknowledged the work provided by Dr. Christopher Austin at NHGRI and Dr. Linda Brady at NIMH in moving this initiative forward.

Another Roadmap activity—re-engineering the clinical research enterprise—is one that includes the participation of several NIH Institutes. Within 8 to 10 years, this initiative expects to build an infrastructure that will facilitate an integrated, safe, and efficient transition from bench research to bedside—and back. An initial priority is to establish a network of 20 to 30 Regional Translational Research Centers that can be integrated with the current General Clinical Research Center Program to accelerate discoveries by supporting, for example, biostatistics, pharmacogenetics, and clinical pharmacology. National translational research core services—modeled on the National Cancer Institute's successful Rapid Access to Intervention Development (RAID) initiative (see http://grants2.nih.gov/grants/guide/notice-files/NOT-CA-03-003.html)—will be established to prepare novel reagents, test animal toxicity, and provide other preclinical assistance. NIMH, as part of the thrust to improve the assessment of clinical outcomes, will take the lead on the development of better quality-of-life measures and surrogate markers for disease outcomes. Additional efforts will focus on harmonizing the varied regulatory processes that often impede the conduct of clinical studies, on integrating clinical research networks, and on creating national virtual repositories that will facilitate communications between clinical trials and large clinical research programs.

Turning to recent advancements in science, Dr. Insel highlighted two studies. The first provides evidence for the importance of gene-environment interactions and how genetic makeup can moderate responses to environmental insults. Earlier studies of how chronic stress contributes to the onset of depression have fastened on a specific gene, 5-HTT, a serotonin transporter (also known as SERT) that codes for the protein that reabsorbs serotonin into the presynaptic terminal and has at least 27 variants. The serotonin promoter polymorphism (5-HTTLPR) has both a "short" and a "long" form that are not found in the gene's coding region but upstream in the regulatory area where they control whether or not—and where—the gene turns on.

This summer, NIMH grantees Drs. Avshalom Caspi and Terrie Moffitt and colleagues published a paper examining this serotonin transporter in conjunction with the onset of depression in a well-characterized sample of 1,037 persons in Dunedin, New Zealand, who were followed for many

years and had experienced multiple episodes of stress. The investigators discovered a straightforward correlation between the "short" and "long" forms of the SERT gene and how participants responded to stress—namely, that participants with the "short" form produced less of the serotonin protein, had fewer reuptake transporter molecules on the presynaptic serotonin terminals, reported a 5-year history of three or four life stressors, and were likely to develop depression. By contrast, participants with a "long" form of the gene were remarkably depression resistant, even if they had endured four similarly measured episodes of severe life stress in the same period (see Caspi, A., Sugden, K., Moffitt, T.E., Taylor, A., Craig, I.W., Harrington, H., McClay, J., Mill, J., Martin, J., Braithwaite, A., and Poulton, R. "Influence of Life Stress on Depression: Moderation by a Polymorphism in the 5-HTT Gene." S*cience* 301:386-389, 2003).

Dr. Insel then discussed another notable scientific discovery with implications for the treatment of depression. While scientists have long observed that antidepressants increase adult hippocampal neurogenesis, Dr. Ronald Duman at Yale University recently narrowed the focus to antidepressants' stimulation of neurogenesis in the hippocampus. In collaboration with another NIMH grantee, Dr. Rene Hen at Columbia University and other colleagues, Dr. Duman observed that the eating behavior of normal mice that have been treated with antidepressants (e.g., fluoxetine, imipramine, or desipramine) for about 28 days showed significant improvement in an animal model of antidepressant effects (treated mice ate more rapidly when placed in a novel environment than their unmedicated counterparts) (see Santarelli, L., Saxe, M., Gross, C., Surget, A., Battaglia, F., Dulawa, S., Weisstaub, N., Lee, J., Arancio, O., Belzung, C., and Hen, R. "Requirement of Hippocampal Neurogenesis for the Behavioral Effects of Antidepressants. *Science* 301:805-809, 2003). This effect did not appear to be related to increased hunger while taking antidepressants.

To confirm the relationship between increased neurogenesis and change in eating behavior, the investigators used a lead shield to irradiate different parts of experimental mouse brains. After proving that irradiation, by itself, did not affect the eating behavior of mice in a novel environment, the investigators demonstrated that hippocampal irradiation completely blocked both neurogenesis and the behavioral effect on eating in mice that had been established on an antidepressant regimen. By contrast, mice that received sham irradiation before being treated with fluoxetine or imipramine for 28 days had a substantially reduced latency period before eating again in a new environment. Using an elegant set of controls, the investigators further demonstrated that irradiating other parts of the mouse brain had no effect on eating latency. The cells produced in the hippocampus are apparently critical for antidepressants' behavioral effects. A related experiment affirmed that 11 to 28 days of antidepressant medication also changed the grooming behavior of mice and that neurogenesis blockade obstructed that behavioral effect. Although it is not yet known whether humans react in the same way, the findings parallel the chronology of the usual 28-day clinical response of patients to antidepressants. This is the first study to provide credence to the proposed role of such neurogenesis in lifting mood.

To conclude, Dr. Insel recalled a recent scientific discovery by investigators at the Institute's Intramural Research Program (IRP), which has led to a new initiative on genetics and schizophrenia. Since Dr. Daniel Weinberger reported to Council a year ago about his—and others'—studies of the association between variations in specific genes and vulnerability to schizophrenia and changes in cognitive performance, the pace of discovery in this area has escalated exponentially. Instead of two or three genes associated with schizophrenia susceptibility, eight or nine have not only been reported but also replicated by three other

laboratories in different cohorts. Although a single gene on this list may confer only 2 to 3 percent of someone's vulnerability for schizophrenia, the variations are relatively frequent and, collectively, could have an important impact. New knowledge is needed about how multiple susceptibility alleles with small effects may induce subtle cell abnormalities, which in turn contribute to abnormal information processing and impact complex functional behavior.

The new program will expand research on the genetics of schizophrenia and will be directed by Dr. Weinberger. Multidisciplinary teams using mouse, fruit fly, and cell culture models, as well as clinical studies and brain imaging, will tease apart how the vulnerability genes work at the molecular, cellular, and systems levels to discover the "risk architecture" of schizophrenia. Rather than relying on traditional clinical features of the illness, the teams will pursue changes in the brain underlying the altered thinking and emotionality associated with the illness. While the IRP will take the lead on gene discovery and translating findings into cell biology, systems biology, and, ultimately, into human studies, a large extramural effort will concentrate on the clinical aspects of this disorder. The extramural commitments include a $40 million investment in four new Conte Neuroscience Centers for Translational Research (at the University of North Carolina, the Mt. Sinai School of Medicine, Yale University, and the University of Pittsburgh); $2.5 million in support for the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative that is directed at defining new cognitive targets for treatment development; and $10 million to fund grants to be awarded through the Treatment Units for Research on Neurocognition and Schizophrenia (TURNS) network for investigations of cognitive abnormalities associated with schizophrenia (see http://www.nimh.nih.gov/grants/SynopNIMH03DM0003.cfm). Other support for research on schizophrenia is provided through the clinical trials program in the Division of Services and Intervention Research (DSIR), which includes the contracted Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project on schizophrenia (see http://www.nimh.nih.gov/studies/catieschiz.cfm) and the large portfolio of other research grants that investigate various aspects of the illness.

Discussion

To Dr. Ming Tsuang's question about the accuracy of bioinformatic methods for RNA profiling, Dr. Insel remarked that a new approach developed by Dr. Sidney Brenner, massively parallel signature sequencing (MPSS), may offer a better fidelity profile of the active RNA species. Dr. Weinberger elaborated that theoretically, MPSS—a synthesis-based approach to transcriptome analysis—can identify the entire molecular transcriptome of a cell, down to one or two mRNA molecules. Since many of the psychiatric disorder risk profile phenotypes reflect subtle changes in expression—on the order of 20 to 40 percent rather than the five- to ten-fold differences found in cancer cells—the higher sensitivity threshold of MPSS may be able to overcome limitations of most hybridization-based assays.

To a question from Dr. Megan Gunnar about whether the environmental regulation of gene expression at different points in development will be considered, Dr. Weinberger responded that genes were selected as a starting point for understanding pathogenesis and risk because they reflect a concrete aspect of negotiating the environment. Once the genetic risk architecture is defined, models need to be developed, both in animals and in large human epidemiological studies, to determine the impact of variations in environmental factors throughout development.

Dr. Eric Nestler, underscoring the importance of the molecular libraries initiative, observed that all currently marketed psychiatric medications focus on fewer than 10 protein targets out of several hundred thousand to a million potentially available ones. The new effort by NIMH is essential to break out of this restricted venture. Dr. Insel commented that the initiative will gain momentum with the start-up of an intramural laboratory and that broad plans include partnering with the pharmaceutical industry and the academic community.

In reply to a question from Dr. Javier Escobar regarding whether, given the shortcomings of psychiatric diagnoses, initiatives are planned for improving knowledge of phenotypes, Dr. Insel explained that a big investment by extramural investigators in both laboratory and human clinical studies will be critical to an increased understanding of endophenotypes and phenotypes and the behavior and cognition effects of these cellular- and systems-level perturbations.

Since the schizophrenia initiative is expected to have a major impact on consumers, mental health delivery systems, treatment providers, and State authorities, Ms. Renata Henry urged NIMH to disseminate information about and encourage feedback on this initiative from all stakeholders. Dr. Insel agreed that effective communications are a critical aspect of the planning.

COUNCIL WORKGROUP ACTIVITIES

- **Treatment Development Workgroup: An Update**

Dr. Wayne Fenton, Deputy Director for Clinical Affairs, Division of Mental Disorders, Behavioral Research and AIDS (DMDBA), opened his presentation on the activities of the Council's Treatment Development Workgroup by noting that during the past 18 months, NIMH has been supporting new initiatives to define new molecular and clinical targets for the development of new medications for schizophrenia.

The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) project (see http://www.matrics.ucla.edu/) has two major goals: to develop a measure of cognition that will serve as an endpoint in clinical trials and to generate methods for assessing cognition that can be used by the pharmaceutical industry and embraced by the Food and Drug Administration as a prerequisite for drug registration.

In late September, a RAND panel will convene to select specific neuropsychological tests that will comprise a NIMH battery for assessing cognition and schizophrenia. Dr. Fenton noted that a MATRICS subcommittee has been formed to select proxy measures of real-world functioning (e.g., negotiating public transportation systems or grocery shopping) that could be co-endpoints in clinical trials along with neuropsychological functioning status measured by the test battery. A psychometric study of that battery will be initiated immediately thereafter in an attempt to reduce the test to the minimal components with the greatest reliability and utility in detecting pharmacological signals. Once the new NIMH test battery is finalized, the goal is to make it available to investigators and pharmaceutical companies that can use it for testing new medications. Relatedly, a new Request for Proposals has been released (see http://www.nimh.nih.gov/grants/indexcon.cfm#RequestforProposal) to established the Treatment Units for Research on Neurocognition and Schizophrenia (TURNS) program—a national resource

that will support studies in a prompt and cost-effective manner to determine the efficacy and safety of novel compounds that target the cognitive deficits associated with schizophrenia.

Dr. Ellen Stover, Director, DMDBA, said that much of the work described by Dr. Fenton originated out of the deliberations of the Council's Clinical Treatment Workgroup. The Workgroup was convened in 2001 by the NIMH Director and the Council to identify areas where NIMH can complement and enhance industry efforts to develop better treatments for mental illnesses. Dr. Stover asked for Council's interest in reconstituting the Workgroup. She noted that the Institute's treatment development efforts cut across all three extramural divisions, including other research activities within DMDBA, basic molecular work in the Division of Neuroscience and Basic Behavioral Science (DNBBS), and large-scale effectiveness trials in DSIR.

Discussion

Dr. Jeffrey Lieberman commented that the Institute has a concerted and sustained plan to enter the arena of therapeutics research. It is clear that treatment development begins at the discovery level—with the molecular libraries effort—and moves to the drug development processes underway in DNBBS, to developing treatments for previously undefined indications such as cognition in schizophrenia, which can be vetted in the real world through, for example, the multi-center clinical trials supported in DSIR.

Dr. Robert Freedman opined that the cognition program has had the unintended benefit of provoking the pharmaceutical industry to expand beyond a focus on dopaminergic antagonists for schizophrenia to consideration of a wider range of molecular targets.

When Dr. Insel asked for comments regarding the Council's Treatment Development Workgroup, Mr. McNulty replied that such a Workgroup would be appropriate to help integrate ongoing efforts. Dr. Tsuang added that future efforts also must encompass the negative symptoms of schizophrenia, including maladaptive withdrawal behaviors and the inability to adjust to society.

Dr. Fenton interjected that this is precisely the type of guidance sought from Council—assistance with selecting scientific opportunities for moving from research on systems and cells into treatment development.

- **Clinical Trials Workgroup: An Update**

Dr. Jeffrey Lieberman, Professor and Vice Chairman of the Department of Psychiatry at the University of North Carolina, Chapel Hill, reported on the progress of Council's Clinical Trials Workgroup, which has been reviewing the clinical treatment research portfolio of DSIR. The Workgroup's charge was to: (1) identify deficiencies, critical knowledge gaps, and overlooked scientific opportunities and recommend ways to address these problems; and (2) assess the progress achieved by active grants and contracts and recommend performance enhancement mechanisms. To date, the Workgroup has conducted a series of planning teleconferences and two portfolio review meetings. Further analyses of the portfolio, with consultation from relevant experts, are underway.

The Workgroup has learned that of the 117 grants and contracts that provide support for clinical trials (not including K awards, small grants, and Center awards), 53 ($53.9 million) primarily

pertained to studies of adults, 44 ($35 million) to studies of children, and 19 ($12.3 million) to studies of the elderly. In terms of disorders, depression accounts for the largest number and percentage of awards (31 percent), followed by anxiety disorder (18 percent) and schizophrenia (12 percent). The disorders with consistently lower numbers and proportions of awards are bipolar disorder (6 percent), dementia (5 percent), autism (4 percent), and a substantial number in the "other" category (includes eating disorders, borderline and other personality disorders, somatoform disorder, and sleep disorders). In terms of funding, of the total $101.2 million support for clinical trials, nearly one-quarter of the budget or $23.8 million is currently allocated to five contracts that have involved the academic community and are now entering their final 2 years: Treatment for Adolescents with Depression Study (TADS), the Sequenced Treatment Alternatives to Relieve Depression (STAR*D), the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) studies of schizophrenia and Alzheimer's disorder, and the Multimodal Treatment Study of Children with Attention-Deficit/Hyperactivity Disorder (MTA) (see http://www.nimh.nih.gov/studies/index.cfm for a description of these trials).

The preliminary findings of the Workgroup are:

- DSIR's research portfolio reflects good scientific quality, reasonable balance, and diversity in the range of disorders and conditions in age-relevant populations that are treated with clinically indicated somatic, pharmacologic, and psychosocial modalities.

- The portfolio lacks breadth and depth across some major disorders (e.g., bipolar disorder and anorexia) and inadequately targets some aspects of public mental healthcare, notably polypharmacy and widespread comorbidity among substance abuse, psychiatric, and other medical disorders.

- Some research redundancy is apparent (e.g., studies of electroconvulsive therapy) as well as continuing emphasis on areas of decreasing clinical relevance (e.g., tardive dyskinesia).

- Some studies are not progressing as originally proposed (e.g., not meeting enrollment targets within the approved timeframe).

To remedy these deficiencies, the Workgroup recommends that:

- DSIR should maximize the efficiencies of treatment research by creating core resources, procedures, and infrastructures within DSIR that support extramural investigators by garnering input from the extramural field as well as establishing active linkages with major stakeholders (e.g., public mental healthcare administrators, consumers, and advocacy groups) and use a variety of funding mechanisms.

- NIMH needs to set a public mental healthcare research agenda that is congruent with public mental health burden and scientific opportunity and proactively support its implementation, recognizing that services and intervention research are inherently more costly and larger scale than many other areas of research funded by NIMH.

- NIMH must set priorities for allocating resources and supporting various dimensions of therapeutics research, including drug development, investigation of treatment mechanisms, and the evaluation and optimization of existing treatments.

Discussion

Dr. Insel said he looked forward to the Workgroup's report and commented on the importance of ensuring input from many stakeholders in both the preparation and the implementation of the recommendations contained in the Workgroup's report.

When Dr. Susan Folkman noted the continuing problem of subject recruitment in clinical trials and suggested that representatives from health maintenance organizations and similar healthcare provider organizations be included as stakeholders, Dr. Lieberman agreed and noted that while communications have been initiated with the National Association of State Mental Health Program Directors (NASMHPD), linkages to private provider groups also should be established. Dr. Insel added that Dr. Grayson Norquist, Director, DSIR, serves on both the Clinical Trials Workgroup and on the NIH Roadmap effort in this area.

Dr. Karen Wagner stressed the urgent need for studies on the safety and efficacy of long-term medication use in young children, as well as in adolescents, and recommended these be added to the pediatric portfolio.

Ms. Renata Henry underscored the importance of developing a closer partnership between NIMH and NASMHPD, which represents all State mental health authorities and much of the public mental health system. She urged the Workgroup to act quickly in making recommendations about the large contracted clinical trials since these represent 25 percent of the current portfolio and will be winding down shortly. Dr. Insel responded that discussions are underway concerning the future of the contracted clinical trials and that he welcomed suggestions from Council and stakeholders.

- **Aging Research Workgroup: Final Report**

Dr. Charles Reynolds, III, Professor, Department of Psychiatry, Neurology, and Neuroscience, University of Pittsburgh Medical School, outlined the findings of the Council's Aging Research Workgroup's final report "Mental Health for a Lifetime: Research for the Mental Health Needs of Older Americans." After acknowledging the contributions of the Council members who participate on the Workgroup, several NIMH staff members, staff at the National Institute on Aging (NIA), and members of the NIMH Aging Research Consortium, Dr. Reynolds recalled the rationale for the report as the increasing public health significance of mental disorders in old age. An already aging population in the United States is expected to double over the next 20 years—from about 35 to 70 million persons. Although effective treatments for mental illnesses exist, they are not adequately disseminated, and the chronic nature of mental illnesses among the elderly portends growing medical costs.

The Workgroup was charged with assessing the Institute's portfolio in mental health and aging research and training with a view to: (1) identify promising areas for further study; (2) develop more researchers who are skilled in these areas; (3) enhance the expertise of NIMH

program staff in aging research; and (4) specify areas for cross-Institute collaborations. In addition to reviewing the relevant NIMH and NIH portfolios and investments in this area for FY 2002, the Workgroup scrutinized relevant consensus statements, including the Depression and Bipolar Support Alliance statement on diagnosis and treatment of mood disorders in old age (see *Archives of General Psychiatry* 60:664-672, 2003) and the IOM's 2002 report "Reducing Suicide: A National Imperative" (see http://books.nap.edu/books/0309083214/html/index.html).

The Workgroup found that NIMH devoted 8.5 percent of its FY 2002 research budget to mental health and aging research, which compares favorably to an average 8.1 percent investment by all other NIH Institutes (or an average of only 4.6 percent if the NIA's budget is subtracted). Nonetheless, the NIMH investment in aging research is inadequate in light of the aging population's current and projected mental health needs over the next two decades. While the greater focus on prevention in the portfolio was commended, the Workgroup noted that the science now exists to promote healthy aging, to reduce suicide among this group, to extend the evidence base for treating severe mental disorders in old age, to decrease the disparities in treatment access encountered by older Americans from minority groups, and to follow promising leads in age-related behavioral neuroscience.

Dr. Reynolds described seven broad principles that provide a context for the specific recommendations that will follow:

1. A life-span approach is vital to understanding mental health and illness.
2. It is important to understand successful or healthy aging as well as the causes, course, and consequences of mental illnesses in later life.
3. Effective preventive interventions in late-life mental illnesses are greatly needed.
4. Further research on the unique aspects of mental disorders in aging populations—such as age- and illness-related changes in pharmacokinetic and pharmacodynamic processes, cognition, social resources, and medical comorbidities—is needed to understand treatment response variability in old age and to improve the care of older people with mental illnesses.
5. The aging brain presents unique opportunities for scientific research on mental illness and mental health.
6. The NIMH portfolio of psychogeriatric research must effectively address the need for better prevention and treatment interventions in mental disorders of late life.
7. Knowledge born of NIMH-sponsored psychogeriatric research must be broadly disseminated to the benefit of all older Americans and their caregivers.

The Workgroup's extensive review of the Institute's research portfolio and staffing yielded a clear picture of the Institute's strengths and areas ready for development. The report offers 11 recommendations that pertain to 4 dimensions of NIMH's geriatric mental health research and training agenda:

1. Build the geriatric mental health research portfolio. Issue a Request for Applications (RFA) to establish interdisciplinary networks of basic and clinical researchers that focus on geriatric mental health questions; encourage administrative supplements that foster the addition of geriatric samples to current clinical grants; and establish repositories for efficient use of geriatric resources (e.g., brain banking activities).

2. Develop geriatric researchers. Issue an RFA that solicits geriatric-mentored K awards; promote the use of the NIH loan repayment program; establish a supplement program that allows current NIMH grantees to add investigators who undertake geriatric research; and become a catalyst for professional associations, educators, and credentialing authorities to develop training models for geriatric research.

3. Organizational recommendations at NIMH. Establish a focal point to oversee and promote the aging portfolio and encourage collaboration across NIH Institutes, particularly with NIA.

4. NIMH staffing needs. Provide training that helps program staff members enhance their expertise in geriatric mental health and continue supporting the activities of NIMH's Aging Research Consortium in promulgating geriatric research interests.

Discussion

Mr. James McNulty urged NIMH to promote more collaboration between the academic research community and the public mental health system to find better treatments and supports for elderly mentally ill persons who are ending up in nursing homes when they might remain in the community without overburdening the Medicaid system.

To a question from Dr. Henry Lester regarding the availability of support for pharmacokinetic research among the elderly, Dr. Reynolds replied that research in this area is limited, although Dr. Bruce Pollock has been an advocate for such research at the University of Pittsburgh.

Dr. James McClelland, pursuing the issue of trans-Institute collaborations, asked whether NIA would partner in joint funding of projects pertaining to the elderly and whether such efforts would be part of the 5 to 10 percent of the budget diverted to the NIH Director's office. He also questioned whether the centralization of trans-Institute projects might foster a few large-scale "Manhattan Projects" rather than smaller, bridging research efforts that also are needed.

Dr. Insel responded that NIH is committed to more trans-Institute collaborations in an effort to promote the best biomedical research that will impact public health and that it is critical for NIMH to participate in those activities, particularly those that implicate mental health.

Dr. Bruce Cuthbert, head of the NIMH Aging Research Consortium, explained that collaboration across Institutes can be fostered by the co-funding of projects. For example, the Healthy Brain Project is assessing the epidemiology of healthy aging in both cognitive and emotional domains with the goal of undertaking new initiatives or incorporating new measures into future initiatives in a cost-effective way—either through shared projects or separate efforts by each Institute. Adding depression measures to ongoing studies of mild cognitive impairment and vice versa can substantially increase knowledge about the interaction of these processes.

Dr. Ming Tsuang remarked that NIA focuses on the normal aging process while NIMH is most concerned with mental illness. Thus, NIA can potentially provide data on normal comparison groups for NIMH studies of aging.

Dr. Anand Kumar, American Association of Geriatric Psychiatry, endorsed the recommendations offered in the Workgroup's final report and supported the establishment of a reconstituted aging branch within NIMH that could interface effectively with the external scientific world, encourage more geriatric investigators, and stimulate more R01s and broader initiatives focused on the aging brain.

Dr. Insel agreed that this may be an opportune time for considering an aging branch to explore many of the issues outlined in the Aging Research Workgroup's report. He also commented on the importance of setting research priorities given the likely leveling off of the Institute's research budget.

Acceptance of the Aging Research Workgroup's Final Report

A motion to accept the final report of the Council's Aging Research Workgroup was requested by Dr. Insel and duly made, seconded, and unanimously approved without further discussion.

New Council Workgroup on Basic Research

Dr. Insel requested Council members' advice on the formation of a new basic science workgroup. Dr. Megan Gunnar elaborated that setting priorities among the increased number of grant applications is particularly challenging now that the budget has leveled off. Although criteria for selecting applied research applications are being formulated, similar guidance regarding the basic research portfolio has not been available. She proposed that Council establish a new workgroup with a mission to: (1) articulate, for NIMH and the public, the role of basic molecular, behavioral, and cognitive research in the Institute's agenda; (2) develop recommendations and guidelines for prioritizing basic research needs; and (3) continue to review and recommend strategies for linking the basic research portfolio with applied efforts to enhance mental health and to prevent, intervene, and treat mental disorders. Council members unanimously supported the formation of the new workgroup

PROGRESS IN DRUG ABUSE AND MENTAL HEALTH RESEARCH

Dr. Nora D. Volkow, the newly appointed Director of the National Institute on Drug Abuse (NIDA), was introduced by Dr. Insel as a world leader in drug addiction research. Dr. Insel noted that her numerous accomplishments have garnered Dr. Volkow many awards, including election to the Institute of Medicine and selection as "Innovator of the Year 2000" by *U.S. News and World Report*.

Dr. Volkow, after welcoming the opportunities for collaboration and innovation with NIMH, reviewed NIDA's mission statement and outlined three priority research areas at NIDA: prevention, treatment interventions, and training researchers.

Prevention research, she elaborated, is targeted toward minimizing the chances that at-risk persons, particularly children and adolescents, start taking drugs or become addicted. A balanced prevention research portfolio has several important facets: (1) identifying genes that make someone more vulnerable to—or better protected against—drug addiction; (2) understanding

developmental changes in the brain that may contribute to youngsters' higher vulnerability for drug abuse and addiction; (3) examining environmental conditions that are suspected risk factors—such as stress and socioeconomic deprivation—as well as the neurobiological consequences of particular environments and how these translate into a higher propensity for drug self-administration; and (4) elucidating the important role of comorbidity in increasing vulnerability to addiction.

Dr. Volkow presented the results from a 1999 morphological study of the brain (see Sowell, E.R., Thompson, P.M., Holmes, C.J., Jernigan, T.L., and Toga, A.W. "In Vivo Evidence for Post-Adolescent Brain Maturation in Frontal and Striatal Regions." *Nature Neuroscience* 2(10): 859-861, 1999) showing that brain maturation between adolescence and young adulthood was distinct from earlier development and was localized in the frontal lobe and subcortical regions of the brain. She commented that these findings may have implications for both schizophrenia and drug addiction, which target the same brain regions. An underdeveloped anterior cingulate gyrus in the frontal cortex, for example, might explain adolescents' relative lack of inhibitions and vulnerability to group peer pressure.

In an elegant study of how the environment can affect the brain's neurobiology, Dr. Michael Nader and colleagues at Wake Forest University studied brain dopaminergic function in individually housed and in socially housed cynomolgus macaques and found that while the monkeys did not differ during individual housing, social housing increased the amount or availability of dopamine D2 receptors in dominant monkeys and produced no change in subordinate monkeys (see Morgan D., Grant K.A., Gage H.D., Mach R.H., Kaplan J.R., Prioleau O., Nader S.H., Buchheimer N., Ehrenkaufer R.L., and Nader M.A. "Social Dominance in Monkeys: Dopamine D2 Receptors and Cocaine Self-Administration." *Nature Neuroscience* 5:169-174, 2002). The investigators went on to note that these neurobiological changes had an important behavioral influence as demonstrated by the finding that cocaine functioned as a reinforcer in subordinate but not dominant monkeys. The investigators concluded that a social variable—the stressor of hierarchical structure—produced a neurobiological change associated with a changed propensity for cocaine self-administration and that an increase in D2 receptors may, by itself, discourage drug self-administration.

To pursue this point, Dr. Volkow referenced her earlier work examining the extent to which dopamine D2 receptors protect against drug self-administration. When a Sprague-Dawley mouse that self-administers alcohol to the point of addiction is injected in the nucleus accumbens with an adenovirus containing the D2 receptor, its D2 receptors increase 50 percent by the 4th day following the intervention—although these receptor levels rapidly decrease to baseline by day 10. Importantly, this artificial increase in D2 receptors dramatically reduced a mouse's alcohol self-administration by 70 percent, although the duration of this effect was short-lived as the receptor levels returned to baseline. This experiment reaffirmed the finding that D2 receptors can serve as a protective factor against drug administration and helps to explain data from epidemiological studies that consistently associate socioeconomic deprivation—a high stressor that seems to reduce D2 receptor levels—with vulnerability to drug addiction.

The increased vulnerability to drug addiction displayed by persons with comorbid mental disorders was compellingly demonstrated by Dr. Darrel Regier and associates a decade ago (see

Regier, D.A., Farmer, M.E., Rae, D.S., Locke, B.Z., Keith, S.J., Judd, L.L., and Goodwin, F.K. "Comorbidity of Mental Disorders with Alcohol and Other Drug Abuse: Results from the Epidemiologic Catchment Area (ECA) Study." *Journal of the American Medical Association* 4:2511-2518, 1990). While only 5 percent of individuals in the general population suffer from a singular illicit drug disorder during their lifetime, those with a mental illness have a substantially higher likelihood of having a comorbid drug disorder, with lifetime prevalence rates of 26 percent for persons with schizophrenia, 42 percent for those with antisocial personality disorder, and 35 percent for those with a bipolar diagnosis. The overlap between smoking and the presence of a psychiatric diagnosis is even more startling: 90 percent of persons with alcoholism smoke, as do 85 percent of patients with schizophrenia, and 80 percent of those with depression.
Dr. Volkow reported on a recent presentation by Dr. Robert Freedman's group at the University of Colorado Health Sciences Center reporting that individuals with mental illness buy almost half the cigarettes sold in the United States. Some underlying neurobiological process seems to promote the comorbidity of drug addiction and mental illness.

A second priority for NIDA is to develop new targets for the development of pharmacological interventions. The science and technology exist to develop drugs other than the dopamine compounds that now dominate the market. Among promising targets are cannabinoid-1 antagonists, which, in animal models, interfere with cocaine, heroin, nicotine, and marijuana self-administration by suppressing reinforcing responses. Since the cannabinoid-1 antagonists also interfere with self-administration of food by obese animals, pharmaceutical companies are developing them for use in overweight persons.

Medications that inhibit metabolizing enzymes also are being investigated since persons who do not metabolize alcohol or nicotine readily because of genetic characteristics are unlikely to drink or smoke. Clinical trials are underway in humans to test whether drugs that interfere with nicotine metabolism will decrease subjects' smoking behavior. Corticotrophin-releasing factor (CRF) antagonists that ameliorate the stress response also have generated widespread interest since stress seems to trigger relapse in animal models of addiction and may be a promising way to minimize relapse among drug abusers during rehabilitation.

Another promising path to new treatment interventions defies old notions of human brain rigidity. Neuroscience research is now proving that the adult human brain undergoes plastic changes in response to environmental stimulation. A recent study (see Maguire, E.A., Gadian, D.G., Johnsrude, I.S., Good, C.D., Ashburner, J., Frackowiak, R.S., and Frith, C.D. "Navigation-Related Structural Change in the Hippocampi of Taxi Drivers." *Proceedings of the National Academy of Science* 97(8):4398-4403, 2000) found that the posterior hippocampi of London taxi drivers are significantly larger than those of non-taxi-driver controls—and may be explained by the challenge of memorizing the city's labyrinthic streets since map memory is stored in the posterior hippocampus. This human brain plasticity in response to environmental stimuli has implications for designing cognitive-behavioral interventions to remediate brain changes induced by chronic exposure to drugs of abuse. One brain area that is consistently abnormal (smaller) in cocaine abusers than in normal controls is the orbital frontal cortex (OFC)—the area above the eyes that metabolizes glucose less well after cocaine administration. The challenge is to find behavioral and cognitive interventions that can activate the OFC and help recover some of its

functioning and also to find ways to ameliorate changes in the inhibitory control mechanism of the anterior cingulate gyrus, which addiction markedly disrupts.

In addition to finding effective new medications and cognitive-behavioral interventions, NIDA must expand research on strategies to optimize the rapid translation of scientific discoveries into clinical practices and community treatment services. As described by Drs. Steven Hyman and Wayne Fenton (see Hyman, S.E. and Fenton, W.S. "Medicine. What are the Right Targets for Psychopharmacology?" *Science* 299:350-351, 2003), the total number of citations pertaining to cognition and schizophrenia in PubMed over the past 11 years has dramatically increased—from 70 to 250. But this increased focus has not translated into more clinical trials on the topic, reflecting a blockage in the urgent science-to-service cycle. The problem is even more urgent in the field of drug addiction.

Another serious impediment to bringing medications into practice is the length of time needed to conduct clinical trials. Former NIDA Director Dr. Alan Leshner created the Clinical Trials Network in 1999, a national network infrastructure that facilitates the conduct of clinical trials in multiple sites with a wide variety of populations and fosters the investigation of many addiction-related issues, including comorbidity. NIDA also created a network of seven Criminal Justice Drug Abuse Treatment Centers that encourage studies of persons in prison given that 40 to 45 percent of prisoners have either a mental illness or a drug disorder. These networks provide a broad infrastructure for rapid evaluation of promising treatments in community-based settings across the country.

NIDA is continuing to partner with other Federal agencies, such as SAMHSA and other NIH Institutes, and with other private and public agencies in an effort to inform both clinical practice and public health about the latest science-based findings. Dr. Volkow concluded her presentation by noting that it is increasingly critical for NIMH and NIDA to coordinate efforts given shared interests in complex questions targeting the complex interactions between environmental-social variables and molecular-genetic variables as they relate to both drug abuse/addiction and mental illness.

Discussion

In response to a question from Dr. Elspeth Cameron Ritchie regarding the implications of marked differences in drug use in various countries and cultures, Dr. Volkow noted that much can be learned from international collaborations. Interactions with research programs outside the United States are continuing, including studies in Russia where drug consumption has escalated dramatically with parallel increases in HIV, AIDS, and hepatitis C virus infection. Studies of immigrants to Russia show they have different rates of addiction than long-term residents in their homelands. This underscores the need to phenotype an addicted person's community of origin in addition to his/her genetic heritage.

When Dr. Megan Gunnar commended the inclusion of social interactions, as well as genes and behaviors, among the study targets for understanding addiction and mental disorders, Dr. Volkow attributed this focus to NIDA staff member Dr. Lisa Onkin, who observed that many cognitive decisions are not made by an individual in isolation but in a group situation. Hence, studies need

to ascertain differences in the way a brain responds to its own stimulation as opposed to having a group assess and evaluate decisions.

Dr. Karen Wagner applauded NIDA's priority focus on prevention, particularly in children as well as adolescents. By the time some children reach adolescence, they may require treatment for drug problems that began in early childhood.

Dr. Susan Essock remarked that the Clinical Trials Network and the Addiction Technology Transfer Centers are exemplary models for building community partnerships, not simply with academic institutions but with grass roots programs. NIMH might consider adopting a similar model since the Institute faces the same challenges of moving research into State mental health delivery systems and other practices. Dr. Volkow added that one success of the Clinical Trials Network is that previously competing communities are now working together in academic centers. This clinical infrastructure is already taking advantage of the genome network and identifying subjects who can be studied for comorbidity and genetics.

Dr. Henry Lester reported that California has levied a $.25/pack tax on cigarettes that will be used to initiate a high-quality, tobacco-related disease research program (TRDRP) with study sections modeled after those at NIH and using similar grant application procedures. He urged NIDA staff to work with TRDRP researchers.

THE NATIONAL COMORBIDITY SURVEY REPLICATION

Dr. Ronald Kessler, Professor, Department of Health Care Policy, Harvard Medical School, and Principal Investigator for the original National Comorbidity Survey (NCS) of Prevalence and Correlates of Psychiatric Disorders in the United States, reported on the family of national epidemiological studies that have followed since the original NCS survey (see http://www.hcp.med.harvard.edu/ncs/ for a description of the surveys and related publications).

The baseline NCS, fielded from 1990 to 1992, interviewed over 8,000 participants, aged 15 to 54 years, using a structured interview to assess DSM-III-R disorders. The NCS-2 followed more than 5,000 of the baseline respondents to ascertain predictive or reciprocal associations between mental and substance use disorders. This comorbidity was not ascertained in the original study because many of the relatively young respondents with an early onset disorder had not yet developed a secondary one. The NCS-R was a replication of the baseline NCS and administered the same questions asked in the NCS to a separate sample of about 9,000 Americans, ages 18 years or older, and was designed to provide estimates of the prevalence of mental disorders, to quantify the burdens and social costs of mental disorders and compare these to equivalent costs stemming from physical disorders, and to project rates of unmet need for treatment as well as the rates of treatment adequacy. The NCS-A interviewed 10,000 nationally representative adolescents, aged 12 to 17 years, in their homes, along with 15,000 of their parents.

Dr. Kessler commented that large-scale epidemiological studies are expensive and typically funded but once a decade. Although not mandated, the data from all of the NCS surveys are made available to the public almost immediately, and numerous papers using this resource have

been published by investigators who were not part of the NCS team. These large-scale studies often provide the foundation for social policy decisions.

Regarding the findings from the NCS-R, the Health and Work Productivity Questionnaire, which assesses the cost to employers of hiring people with various kinds of illness, was administered to about 700,000 employees of large American corporations in 2003. Analyses show that untreated depression, adult ADHD, alcoholism, and similar mental disorders have a staggering effect on sickness absences, quality of work, and industrial accidents. In fact, untreated depression leads to more industrial accidents than alcoholism. However, Dr. Kessler pointed out the difficulties inherent in assessing unmet treatment needs. One important feature of the NCS-R, he said, is that it assessed severity of illness (using assessment-embedded items in the survey that translate into standard measurements used in clinical studies, such as the Hamilton Rating Scale for Depression) and the timing of the initiation of treatment (including why people get into and drop out of treatment)—something that has not be assessed in prior surveys. The NCS-R also ascertained modifiable risk factors for the onset and course of mental illnesses, barriers to help seeking, and predictors of treatment dropout and treatment adequacy. With respect to delivery systems, patients leave treatment with a family doctor more often than they stop seeing psychiatrists; they leave talk therapy more frequently than pharmacotherapy; and they are least likely to dropout when treated by both a mental health professional and a family doctor with a combination of psychotherapy and pharmacotherapy.

Treatment adequacy was determined from a series of questions about medication usage and the types and duration of psychological therapies received. The completed analyses for depression demonstrated that a majority of patients being treated for this illness were not receiving appropriate clinical care.

The set of diagnoses in the NCS-R was expanded considerably from the original survey. In addition to anxiety, mood, and substance use disorders, a number of impulse control disorders were added. It appears that as many people in the United States have intermittent explosive disorder (IED) as have panic attacks. While women are twice as likely as men to have panic attacks, men are 2 to 1 more likely to have IED, and IED among males is associated with a maternal history of depression to the same extent that panic attacks among women are associated with a similar maternal history.

The NCS-R also assessed personality disorders and other affective psychoses, eating disorders, and adult separation anxiety disorder for adults as well as the childhood disorders of ADHD, conduct disorder, oppositional defiance disorder, and separation anxiety that have extensions into adulthood. Many adults with a primary ADHD diagnosis have numerous comorbidities, some of which may be explained by looking at their diagnoses retrospectively by age of onset. Some children have a diagnosis of oppositional defiant disorder at a young age, followed by a diagnosis of conduct disorder, and followed by a designation of antisocial behavior that is frequently associated with increased drinking and drug usage, and, by age of 18 years, they become depressed. Another set of youngsters start out life as shy and unassertive until they get depressed and start drinking to self-medicate their mood. By the time they reach the age of 25 years, they end up with a similar set of symptoms and problems as those children diagnosed early on with operational defiant disorder.

The major burden of psychopathology in the United States is concentrated in 5 to 8 percent of the population who meet criteria for numerous mental disorders in any given year. Interestingly, a diagnosis of ADHD in childhood often is associated with a diagnosis of one of the major mental illnesses in adulthood.

The prevalence of severe mental illness (SMI), using the definition for SMI described in the ADAMHA Reorganization Act and the operationalization described by Kessler et al. (see Kessler, R.C., Barker, P.R., Colpe, L.J., Epstein, J.F., Gfroerer, J.C., Hiripi, E., Howes, M.J., Normand, S.T., Manderscheid, R.W., Walters, E.E., and Zaslavsky, A.M. "Screening for Serious Mental Illness in the General Population." *Archives of General Psychiatry* 60:184-189, 2003) has increased by about 20 percent in the last decade, moving from about 5 percent of the population in the NCS to roughly 6 percent of the population surveyed with the NCS-R. This increase occurred despite enormous increases in service utilization during the same time period. Although only 3.9 percent of the population consulted a specialist about a mental health or substance problem in 1990, this figure increased to 6.2 percent by 2000. The percentage of the population seeking help with a mental health problem from a general practitioner increased even more significantly over the past decade in the preliminary NCS-R data—moving from 3.3 percent in 1990 to 9.2 percent in 2000. Help from someone in the human services sector—a social worker, counselor, minister, priest, or rabbi—also increased from 5.4 percent to 7.1 percent. Interestingly, the large increase in the percentage of persons with a mental problem who seek help from general practitioners is related to a patient's symptom severity—the more severe the mental illness, the more likely that someone will enter treatment with a general practitioner. By comparison, the percentage of persons with mental disorders who enter treatment with specialists has not increased significantly over the past 10 years. Compared to 18.1 percent of persons with SMI who received specialty treatment a decade ago, 20.7 percent of patients in this category received specialty care in 2000. Similarly, among persons with SMI, 15.2 percent were treated by mental health professionals in 1990 compared to 16.9 percent in 2000. However, almost double the number of persons with less serious mental illnesses sought specialty treatment in 2000 (4.8 percent) than entered specialty care in 1990 (2.5 percent). This likely reflects the fact that persons with less serious illnesses are more likely to have insurance coverage for treatment and are more likely to see a mental health specialist today than a decade ago. Thus, changes in treatment participation may be driven more by the organization and financing of mental health care than by patients' needs.

Turning to the World Mental Health Initiative, Dr. Kessler explained that he has been working with the World Health Organization (WHO) to foster collaborations among countries that conduct national mental health surveys similar to the NCS. While those countries were collecting a lot of equivalent information about the prevalence of disorders among different age, gender, and education groups, there was little comparability in questions about services or a systematic approach to risk factor analysis. In 1997, a mini-consortium of 10 countries was established to conduct similar expanded mental health surveys under the World Health Initiative. Currently, 28 countries from North America, Latin America, Europe, the Middle East, Africa, and Asian/Pacific areas are interviewing 222,000 people using the NCS-R. Comparative data analyses are being coordinated across all the participating countries, and some are managed through a series of regional workgroups. For example, the Pan American Health Organization workgroup is

combining data from the Latin American countries and working with health policymakers to develop a set of consistent reports that are forwarded to the Ministers of Health in each country. The United States, foundations, the European Union, the pharmaceutical industry, and several other governments provide funding for this $85 million data collection initiative.

To conclude, Dr. Kessler urged NIMH to foster epidemiological and other mental health research by developing a unified strategy for investing in research that fosters creative experimentation without stifling risky innovations and ultimately leads to reducing the burden of mental illness.

Discussion

Dr. Kessler clarified for Mr. Robert Boorstin that all the interviews for the World Mental Health Initiative surveys in the participating countries are conducted face-to-face.

PUBLIC COMMENT

Dr. Steven Zarit from the Pennsylvania State University spoke on behalf of the American Psychological Association to endorse the report by Council's Aging Research Workgroup, particularly the recommendations for increasing NIMH support of research and training related to geriatric mental health, expanding the utilization of K and T awards, linking training to small business initiatives, developing dedicated program staff with expertise in late-life mental illnesses, creating an associate director position for mental health and aging at NIMH, and re-establishing an aging branch to stimulate research.

Dr. Joel Streim, President of the American Association for Geriatric Psychiatry, joined the plea to reconstitute an aging branch within NIMH, saying this would encourage more cross-institute collaborations—especially between NIMH and NIA, stimulate more relevant applications, and help resolve workforce issues. Dr. Ira Katz, representing the American Geriatrics Society, spoke for himself and Carol Ann Schutz, Executive Director of the Gerontological Society of America, to support the recommendations of the Council's Aging Research Workgroup.

Dr. Joan Levy Zlotnik, Executive Director of the Institute for the Advancement of Social Work Research, endorsed the Council's Workgroup report on aging research, especially the focus on older persons in the context of their families and ways that the elderly can overcome depression. She added that NIMH support for social work research between 1993 and 2000 inspired formation of the Institute she represents and fostered useful attention to issues surrounding aging and services.

Dr. Ann Kearney-Cooke, Director of Public Affairs for the Academy of Eating Disorders, agreed that anorexia nervosa is an underfunded disorder, noting that persons with this diagnosis have the highest mortality rate of any mental illness as well as the highest rates of short- and long-term physiological consequences. Dr. Kearney-Cooke asked Council to consider forming a workgroup on prevention and treatment of eating disorders since public attention currently aimed at obesity could increase concerns about weight, and dieting can unintentionally lead to other eating problems.

Dr. Richard Birkel, Executive Director for the National Alliance for the Mentally Ill, endorsed NIMH's commitment to prospective longitudinal studies that help researchers understand biological-environmental interactions; services and treatment research that informs Medicaid decisions about effective medications; the use of contracts to fill gaps in the research portfolio; continuation of the CATIE project; research on neglected aspects of the lifespan—particularly mental disorders in the very young and very old; reconstituting an aging branch at NIMH; encouraging young investigators to enter this field; and the focus on cognitive functioning as a target for rehabilitating persons with schizophrenia.

Dr. Thomas Horvath, from the Congressional Committee for the Seriously Mentally Ill Veteran, pledged the commitment of the Department of Veterans Affairs (VA) to implementing the recommendations of the President's New Freedom Commission on Mental Health (see http://www.mentalhealthcommission.gov/). Dr. Horvath noted that he will participate on a VA workgroup for implementing the Commission's recommendations and that he welcomed suggestions from Council members and NIMH staff. Dr. Horvath reported that Dr. Nelda Wray, Chief Research Development Officer at the VA, and her deputy, Dr. Wendy Eisen, are committed to increasing currently underfunded research on mental illness in the VA portfolio. The Committee for the Seriously Mentally Ill Veteran is working with consumer members from NAMI, the American Legion, Vietnam Veterans of America, and other groups to support Dr. Wray's endeavor to restructure VA medical research, strengthen its clinical impact, improve its translational ability, and pursue cutting-edge neuroscience.

Dr. Alan Kraut, Executive Director of the American Psychological Society, urged NIMH to work toward strengthening the linkage between basic science and treatment. He referenced findings from the journal, *Psychological Science in the Public Interest*, which commissions teams of eminent researchers to review interesting aspects of psychological science. In recent issues, these panels concluded that children should be taught phonemes when they learn to read; that self-esteem—despite its promotion by many schools—is not related to academic achievement, juvenile delinquency, or substance abuse; and that commonly used trauma counseling after a crisis may inhibit recovery. Unfortunately, all too often, many interventions are not empirically validated and have little connection to basic behavioral science, cognition, and developmental or social psychology.

Ms. Valerie Porr, President of Treatment and Research Advancements National Association for Personality Disorder (TARA NAPD), thanked NIMH for reissuing the RFA for borderline personality disorder and acknowledged the critical importance of including personality disorders in the NCS-R. Dr. Kessler's observation that the average age of onset for mental illness in America is 15 years confirms the experience of NAPD's helpline that receives calls from adolescents all over the nation who cannot access treatment. Personality disorders infuse most mental illnesses and are variously labeled as intermittent explosive disorder, oppositional defiance, conduct disorder, borderline personality disorder, or ADHD. Some studies, such as those conducted by Dr. Carlos Grilo at Yale, have found that 67 percent of adolescents and young adults have comorbid borderline personality and substance abuse diagnoses. Personality disorders also are strongly associated with domestic violence. In response, Dr. Insel credited NIMH staff members Drs. James Breiling, Robert Heinssen, and Bruce Cuthbert for their work on

reissuing the RFA on personality disorders, for championing this cause within NIMH, and for the assistance they provide to investigators in this area.

Dr. Darrel Regier, representing the American Psychiatric Association (APA), reiterated APA's support for funding the highest quality research programs and assured the Council that APA is committed to working with Congress to continue previous investments and approve new commitments for psychiatric research. He also requested support for APA's interest in learning more about phenotypes and undertaking new ways to classify disorders. He cautioned that with the introduction of HIPPA on October 16, the field might revert to adopting DSM-II as the official diagnostic system under ICD-9-CM. This will occur unless DHHS approves some variance of DSM as defining appropriate criteria for mental disorders on the payment claims that clinicians submit. Dr. Insel was hopeful that there would be a resolution of this issue prior to October 16.

Dr. Insel ended the meeting on a sad note by mentioning the tragic loss of a close friend and brilliant colleague, Dr. Patricia Goldman-Rakic, a former NIMH scientist and Advisory Council member who was most recently the Principal Investigator of a Conte Center grant. She was one of the brightest stars in the galaxy of people that NIMH has supported and an irreplaceable neuroscience researcher. Recalling her death as an enormous personal loss to family and friends, as well as to the field, Dr. Insel asked Council to take a few moments to remember Dr. Goldman-Rakic and announced that there would be an October 19 memorial service in New Haven.

ADJOURNMENT

After reminding Council of the next meeting on February 5-6, 2004, Dr. Insel adjourned the 204th meeting of the NAMHC at 1:10 p.m. on September 12, 2003.

I hereby certify that, to the best of my knowledge, the foregoing minutes are accurate and complete.

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Thomas R. Insel, M.D., Chairperson